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# Adrenomedullin optimises mortality prediction in COPD patients

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## KEYWORDS

Chronic obstructive  
pulmonary disease;  
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## Summary

**Background:** Current multicomponent scores that predict mortality in COPD patients might underestimate the systemic component of COPD. Therefore, we evaluated the accuracy of circulating levels of proadrenomedullin (MR-proADM) alone or combined with the ADO (Age, Dyspnoea, airflow Obstruction), updated ADO or BOD (Body mass index, airflow Obstruction, Dyspnoea) index to predict all-cause mortality in stable COPD patients.

**Methods:** This study pooled data of 1285 patients from the COMIC and PROMISE-COPD study.

**Results:** Patients with high MR-proADM levels ( $\geq 0.87$  nmol/l) had a 2.1 fold higher risk of dying than those with lower levels ( $p < 0.001$ ). Based on the C-statistic, the ADOA index

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(ADO plus MR-proADM) ( $C = 0.72$ ) was the most accurate predictor followed by the BODA (BOD plus MR-proADM) ( $C = 0.71$ ) and the updated ADOA index (updated ADO plus MR-proADM) ( $C = 0.70$ ). Adding MR-proADM to ADO and BOD was superior in forecasting 1- and 2-year mortality. The net percentages of persons with events correctly reclassified (NRI+) within respectively 1-year and 2-year was 31% and 20% for ADO, 31% and 20% for updated ADO and 25% and 19% for BOD. The net percentages of persons without events correctly reclassified (NRI-) within respectively 1-year and 2-year was 26% and 27% for ADO, 27% and 28% for updated ADO and 34% and 34% for BOD.

**Conclusions:** Adding MR-proADM increased the predictive power of BOD, ADO and updated ADO index.

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## Background

COPD is a main cause of morbidity and mortality. The disease is associated with premature death due to pulmonary complications or associated comorbidities [1].

The assessment of predictors to determine time-to-death probability and other clinically relevant outcomes is a topic of major interest. Although several multicomponent indices are available, larger studies or pooling of data from multiple studies are required to demonstrate external generalisability and robustness of the parameters and indices found.

One well-validated multidimensional tool is the Body mass index, airflow Obstruction, Dyspnoea, Exercise capacity (BODE) index, which is based on the body mass index, FEV<sub>1</sub> % predicted, modified Medical Research Council dyspnoea grade (mMRC), and 6-min-walk distance (6MWD) [2]. Another multidimensional tool is the ADO index, which combines Age, Dyspnoea (mMRC) and airflow Obstruction (FEV<sub>1</sub> % predicted). Both the BODE and the ADO index were recently internationally validated and updated [3,4].

Although both index scores are multicomponent scores, the systemic component of COPD may be under reflected in these scores. The influence of comorbidities in mortality seems to be underestimated by the BODE-index. Accordingly, a disease-specific comorbidities index (COTE index) in addition to BODE has been proposed to improve its mortality prediction in COPD [5]. Furthermore, the BODE has a practical limitation, since it requires a 6-min walking test (6MWT), which makes it more cumbersome in many clinical settings. The use of the BOD, BODE without exercise capacity measurement, has therefore been suggested [6,7].

The predictive quality of current tools might be increased by the inclusion of systemic biomarkers into the multidimensional tools. A very promising biomarker is midrange-proadrenomedulin (MR-proADM). MR-proADM is the more stable precursor of adrenomedulin (ADM), which closely reflects the level of active ADM. MR-proADM has been shown to be an independent predictor of mortality when measured at hospitalisation for an acute exacerbation of COPD (AECOPD) [8] and in stable state [7,9].

Patients presenting with circulating levels of MR-proADM levels above 0.71 nmol/L had a 3-fold higher risk of dying [9]. In patients with stable COPD, MR-proADM plus BODE predicts mortality better than BODE alone. Also, MR-proADM plus BOD predicts mortality more accurately than BODE alone [7].

The primary aim of the present analysis was to evaluate the accuracy of circulating levels of MR-proADM alone or in combination with ADO, the updated ADO or BOD to predict all-cause mortality in a pooled assessment of two large European, prospective observational cohort studies of patients with COPD in stable state.

## Methods

### Setting and study population

This analysis is a pooled analysis of individual patient-data from both the COMIC and PROMISE-COPD study.

The COMIC study is a single centre cohort study from Enschede, the Netherlands. From December 2005 till April 2010, 795 patients were included with a follow-up period of minimally three years.

The PROMISE-COPD study consecutively recruited and followed 638 patients of 11 pulmonology departments of European hospitals from November 2008–October 2011. Detailed in- and exclusion criteria of both studies are included in the [Online supplement](#).

### Outcomes

The primary outcome parameter was survival, based on all-cause mortality. Date of death was verified from public registries.

Spirometry was administered by trained respiratory technicians according to the American Thoracic Society guidelines [10]. Data on common co-morbidities like myocardial infarction, congestive heart failure and diabetes mellitus were obtained from medical records and/or during study visits [11–14]. Patients completed the modified Medical Research Council dyspnoea questionnaire (mMRC) in local languages, in validated versions when

available [15]. The BOD comprises BODE without exercise capacity measurement [6]. The components were scored according to the same cut-offs as in BODE [2]. The BOD therefore ranges from 0 to 7 [7]. The original and updated ADO score ranges, in increasing severity, from respectively 0 to 10 and from 0 to 14 points [3]. The assignment of points for the BOD, ADO and updated ADO are described in the [Online supplement](#). All measurements were performed in stable state.

### Measurement of MR-proADM

MR-proADM levels were measured in plasma obtained at stable state with an automated sandwich immunoassay using a time-resolved amplified cryptate emission technology (TRACE) [16]. Details of the measurement are included in the [Online supplement](#).

### Statistics

Continuous variables are expressed as mean with standard deviation (SD) or median with interquartile range (IQR); categorical variables as counts with corresponding percentages.

We analysed time to death by Kaplan–Meier survival curves.

We used univariate and multivariate Cox proportional hazard regression models to establish the relationship of MR-proADM, the ADO, updated ADO and BOD indices, alone or combined with MR-proADM (i.e. ADOA, updated ADOA and BODA), with all-cause mortality. Furthermore, the C-statistic for the univariate models and the net reclassification improvement was calculated. All tests were two-sided and a p-value of 0.05 or lower was considered statistically significant. Data were analysed using SPSS, version 20 (SPSS Inc. Chicago IL) or R, version 3.0.1. Further detailed statistical information is included in the [Online supplement](#).

## Results

### Baseline characteristics

In total, the studies provided data of a total of 1285 patients in which MR-proADM could be determined. [Table 1](#) compares baseline characteristics of both study populations.

Median follow-up times of the COMIC and PROMISE-COPD study were resp. 915 (824–1068) and 725 (421–764) days. The 1- and 2 year cumulative survival rates were respectively 92.8% and 85.4% for the COMIC study and 94.3% and 89.2% for the PROMISE-COPD study. Overall mortality during follow up was 20.3% (N = 261), of which resp. 205 (30.6%) in the COMIC and 56 (9.1%) in the PROMISE-COPD study.

### Crude mortality risk prediction

The survival curve for the four quartiles of MR-proADM ([Fig. 1](#)), shows that the fourth quartile of MR-proADM

**Table 1** Baseline characteristics of 1285 individuals with stable COPD included in this analysis.

	COMIC N = 671	PROMISE-COPD N = 614	p-value
Mean age in y (SD)	67.3 (9.5)	67.0 (9.5)	0.576
Male (n (%))	404 (60.2)	432 (70.4)	<0.001
Current smoker (n (%))	170 (25.3)	204 (33.4)	0.002
Mean pack-years (SD) <sup>a</sup>	37.7 (22.9)	50.8 (29.8)	<0.001
Mean BMI (SD) <sup>b</sup>	27.4 (5.4)	26.0 (5.5)	<0.001
Lung function <sup>c</sup>			
Mean FEV <sub>1</sub> in l (SD)	1.5 (0.6)	1.3 (0.5)	0.001
Mean FEV <sub>1</sub> % pred(SD)	53.6 (19.1)	49.4 (16.7)	<0.001
GOLD stage (n (%)) <sup>d</sup>			<0.001
I	63 (9.4)	16 (2.6)	
II	299 (44.6)	280 (45.8)	
III	252 (37.6)	214 (35.0)	
IV	56 (8.4)	101 (16.5)	
Mean mMRC score (SD) <sup>e</sup>	1.8 (1.3)	1.7 (1.2)	0.776
Mean BOD score (SD) <sup>f</sup>	2.4 (1.8)	2.6 (1.8)	0.163
Mean ADO score (SD) <sup>g</sup>	4.1 (1.8)	4.1 (1.7)	0.769
Mean updated ADO score (SD) <sup>g</sup>	7.6 (2.4)	7.8 (2.2)	0.154
Comorbidities (n (%))			
Congestive heart failure <sup>h</sup>	112 (16.7)	93 (15.2)	0.465
Myocardial infarction <sup>i</sup>	27 (4.0)	58 (9.5)	<0.001
Diabetes mellitus <sup>j</sup>	43 (6.4)	74 (12.2)	<0.001

Abbreviations; SD: Standard Deviation; BMI: Body Mass Index; FEV<sub>1</sub>: Forced Expiratory Volume in 1 s; GOLD: Global Initiative for Chronic Obstructive Lung disease; mMRC: modified Medical Research Council Dyspnoea grade; BOD: Index that combines Body mass, airflow Obstruction (FEV<sub>1</sub>% predicted), Dyspnoea (mMRC); ADO: Index that combines Age, Dyspnoea (mMRC) and airflow Obstruction (FEV<sub>1</sub>% predicted).

<sup>a</sup> Pack-years of resp. 626 and 593 patients in the COMIC and PROMISE-COPD study.

<sup>b</sup> BMI of resp. 658 and 612 patients.

<sup>c</sup> Lung function measures of resp. 670 and 564 patients.

<sup>d</sup> GOLD stage of resp. 670 and 611 patients.

<sup>e</sup> mMRC score of resp. 654 and 599 patients.

<sup>f</sup> BOD score of resp. 642 and 552 patients.

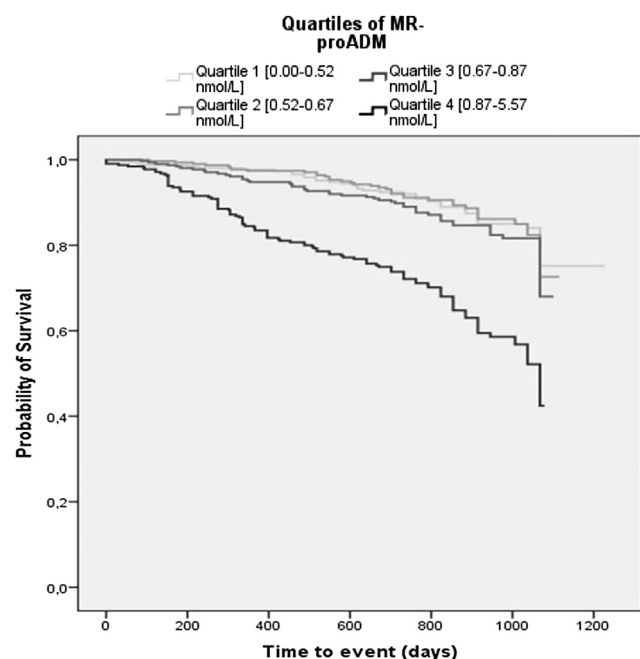
<sup>g</sup> ADO and updated ADO score of resp. 653 and 544 patients.

<sup>h</sup> Diagnosis of congestive heart failure was recorded of 612 patients in the PROMISE-COPD study.

<sup>i</sup> Diagnosis of myocardial infarction was recorded of 611 patients in the PROMISE-COPD study.

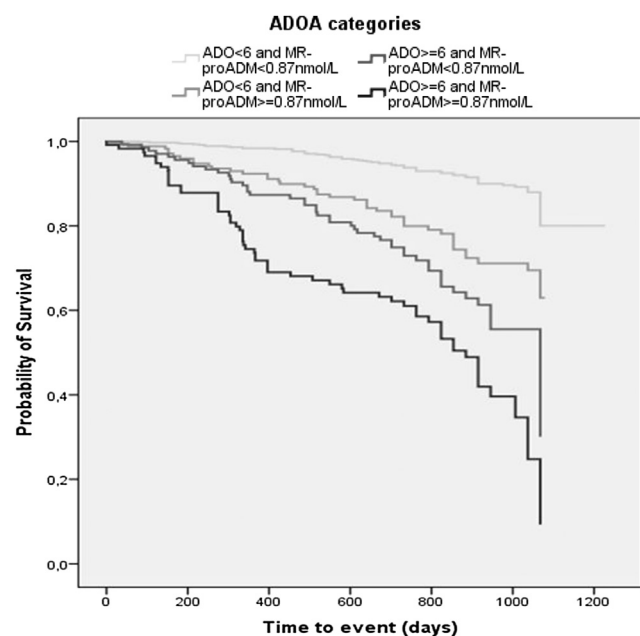
<sup>j</sup> Diagnosis of diabetes mellitus was recorded of 608 patients in the PROMISE-COPD study.

(cut-off at 0.87 nmol/L) was associated with increased mortality ( $p < 0.001$ ). As compared to the first quartile, Hazard Ratios (HRs) of resp. the second, third and fourth quartile were 1.12 (95%CI 0.72–1.74;  $p = 0.617$ ), 1.43 (95%CI 0.95–2.15;  $p = 0.090$ ) and 3.70 (95%CI 2.56–5.36;  $p < 0.001$ ). When MR-proADM level was dichotomised into low (1st–3rd Quartile) and high (4th Quartile) mortality risk, the HR of the high risk compared to the low risk category was 3.1 (95%CI 2.4–4.0;  $p < 0.001$ ).



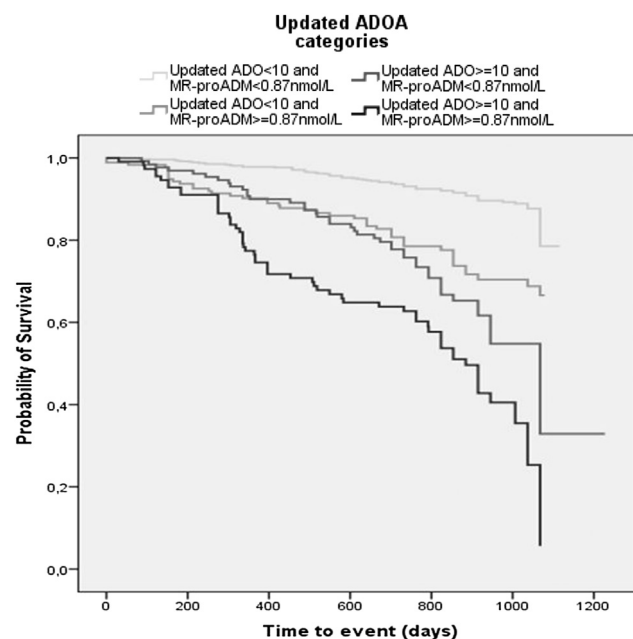
**Figure 1** Kaplan–Meier survival curve for the four quartiles of MR-proADM.

**Fig. 2** depicts the survival curve of the four categories of the ADOA index, which combines low ( $<6$ ) and high ( $\geq 6$ ) mortality risk based on the ADO index with low (1<sup>st</sup>–3<sup>rd</sup> Quartile) and high (4<sup>th</sup> Quartile) mortality risk based on MR-proADM levels. Each increase in ADOA index category was associated with increased mortality ( $p < 0.005$ ). As compared to the low/low risk category, HRs were 2.8 (95% CI 1.9–4.0) 4.8 (95% CI 3.4–6.8) and 8.7 (95% CI 6.3–12.0) (all  $p < 0.001$ ).



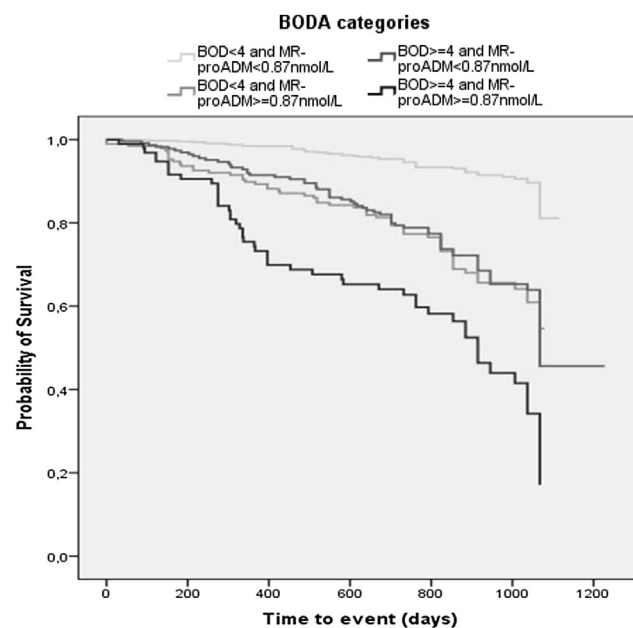
**Figure 2** Kaplan–Meier Survival Curve for the “ADOA” categories.

**Fig. 3** presents four categories of the updated ADOA index, which combines low ( $<10$ ) and high ( $\geq 10$ ) mortality risk based on the updated ADO index with low (1<sup>st</sup>–3<sup>rd</sup> Quartile) and high (4<sup>th</sup> Quartile) mortality risk based on MR-proADM levels. Also with the updated ADOA index each increase in category was associated with increased mortality ( $p < 0.021$ ). As compared to the low/low risk category, HRs were 2.6 (95% CI 1.8–3.7) 4.2 (95% CI 2.9–5.9) and 7.9 (95% CI 5.7–10.9) (all  $p < 0.001$ ).



**Figure 3** Kaplan–Meier Survival Curve for the “Updated ADOA” categories.

The survival curve of the four categories of the BODA index (**Fig. 4**) shows that patients with either high mortality risk based on MR-proADM or high mortality risk based on the



**Figure 4** Kaplan–Meier Survival Curve for the “BODA” categories.



**Table 2** Univariate Cox-regression models for all-cause mortality prediction.

	N = 1189	HR	95%CI	p-value	C-statistic
ADO				<0.001	0.67
<6	931	1.0			
≥6	258	4.9	3.8–6.3		
Updated ADO				<0.001	0.65
<10	940	1.0			
≥10	249	4.5	3.5–5.8		
MR-proADM				<0.001	0.64
Quartile 1–3	896	1.0			
Quartile 4	293	3.1	2.4–4.0		
BOD				<0.001	0.63
<4	855	1.0			
≥4	334	3.2	2.5–4.1		
ADOA				<0.001	0.72
ADO <6 & MR-proADM <0.87 nmol/l	757	1.0			
ADO <6 & MR-proADM ≥0.87 nmol/l	174	2.8	1.9–4.0		
ADO ≥6 & MR-proADM <0.87 nmol/l	139	4.8	3.4–6.8		
ADO ≥6 & MR-proADM ≥0.87 nmol/l	119	8.7	6.3–12.0		
Updated ADOA				<0.001	0.70
ADO <10 & MR-proADM <0.87 nmol/l	763	1.0			
ADO <10 & MR-proADM ≥0.87 nmol/l	177	2.6	1.8–3.7		
ADO ≥10 & MR-proADM <0.87 nmol/l	133	4.2	2.9–5.9		
ADO ≥10 & MR-proADM ≥0.87 nmol/l	116	7.9	5.7–10.9		
BODA				<0.001	0.71
BOD <4 & MR-proADM <0.87 nmol/l	663	1.0			
BOD <4 & MR-proADM ≥0.87 nmol/l	192	3.9	2.7–5.5		
BOD ≥4 & MR-proADM <0.87 nmol/l	233	3.9	2.8–5.4		
BOD ≥4 & MR-proADM ≥0.87 nmol/l	101	8.4	5.8–12.1		

Abbreviations; ADO: Index that combines Age, Dyspnoea (mMRC) and airflow Obstruction (FEV<sub>1</sub>% predicted); Updated ADO: Updated ADO index as suggested by Puhan et al.; MR-proADM: midrange-proadrenomedulin; BOD: Index that combines Body mass, airflow Obstruction (FEV<sub>1</sub>% predicted), Dyspnoea (mMRC); ADOA: Index that combines the ADO index with MR-proADM; Updated ADOA: Index that combines the updated ADO index with MR-proADM; BODA: Index that combines the BOD index with MR-proADM.

BOD index (≥4) had an almost equal increased risk of mortality ( $p = 0.97$ ) compared to the low/low risk category, with HRs of resp. 3.9 (95%CI 2.7–5.5;  $p < 0.001$ ) and 3.9 (95%CI 2.8–5.4;  $p < 0.001$ ). High mortality risk based on both the BOD index and MR-proADM was associated with a further increase in mortality (HR 8.4; 95%CI 5.8–12.1;  $p < 0.001$ ).

Table 2 presents the univariate Cox regression analyses of all indices. Based on the C-statistics of the separate indices and MR-proADM the ADO index was the most accurate predictor (highest C-statistic). Adding MR-proADM to the BOD and both the original and updated ADO improved the predictive power of all three indices. The ADO index was the most accurate predictor followed by the BODA index.

Adding MR-proADM to ADO and BOD showed superior ability to forecast 1-year and 2-year survival and non-survival (see Table 3). The net percentages of persons with events correctly reclassified (NRI+) when adding MR-proADM to the indices within respectively 1-year and 2-year is 31% and 20% for ADO, 31% and 20% for updated ADO and 25% and 19% for BOD.

The net percentages of persons without events correctly reclassified (NRI-) when adding MR-proADM to the indices within respectively 1-year and 2-year is 26% and 27% for ADO, 27% and 28% for updated ADO and 34% and 34% for BOD.

### Multivariable adjusted mortality risk prediction

Table 4 depicts multivariate Cox-regression analyses. After adjustment for confounders, the HR for mortality remained significantly higher in patients with high compared to low mortality risk based on MR-proADM levels (HR 2.1 (95%CI 1.6–2.8;  $p < 0.001$ ).

**Table 3** Net reclassification of survivors and non-survivors.

	NRI+		NRI-	
	1-year	2-year	1-year	2-year
ADOA	31 (8–52)	20 (4–35)	26 (20–32)	27 (21–33)
Updated ADOA	31 (9–53)	20 (4–37)	27 (21–32)	28 (22–34)
BODA	25 (3–47)	19 (3–36)	34 (28–39)	34 (29–40)

Abbreviations; ADOA: Index that combines the ADO index with MR-proADM; Updated ADOA: Index that combines the updated ADO index with MR-proADM; BODA: Index that combines the BOD index with MR-proADM; NRI+ the net percentages of persons with events correctly reclassified; NRI-: the net percentages of persons without events correctly reclassified.

**Table 4** Multivariate Cox-regression models for all-cause mortality prediction.

	N = 1185	HR	95%CI	p-value
ADO <sup>a</sup>				<0.001
<6	929	1.0		
≥6	256	4.3	3.4–5.6	
Updated ADO <sup>a</sup>				<0.001
<10	938	1.0		
≥10	247	3.9	3.0–5.0	
MR-proADM <sup>b</sup>				<0.001
Quartile 1–3	893	1.0		
Quartile 4	292	2.1	1.6–2.8	
BOD <sup>c</sup>				<0.001
<4	853	1.0		
≥4	332	3.0	2.4–3.9	
ADOA <sup>d</sup>				<0.001
ADO <6 & MR-proADM <0.87 nmol/l	756	1.0		
ADO <6 & MR-proADM ≥0.87 nmol/l	173	3.3	2.3–4.8	
ADO ≥6 & MR-proADM <0.87 nmol/l	137	4.3	3.1–6.1	
ADO ≥6 & MR-proADM ≥0.87 nmol/l	119	8.8	6.3–12.2	
Updated ADOA <sup>d</sup>				<0.001
ADO <10 & MR-proADM <0.87 nmol/l	762	1.0		
ADO <10 & MR-proADM ≥0.87 nmol/l	176	3.1	2.2–4.5	
ADO ≥10 & MR-proADM <0.87 nmol/l	131	3.4	2.5–5.1	
ADO ≥10 & MR-proADM ≥0.87 nmol/l	116	7.6	5.5–10.5	
BODA <sup>c</sup>				<0.001
BOD <4 & MR-proADM <0.87 nmol/l	662	1.0		
BOD <4 & MR-proADM ≥0.87 nmol/l	191	2.7	1.8–3.9	
BOD ≥4 & MR-proADM <0.87 nmol/l	231	3.8	2.7–5.3	
BOD ≥4 & MR-proADM ≥0.87 nmol/l	101	5.8	3.9–8.4	

Abbreviations; ADO: Index that combines Age, Dyspnoea (mMRC) and airflow Obstruction (FEV<sub>1</sub>% predicted); Updated ADO: Updated ADO index as suggested by Puhan et al.; MR-proADM: midrange-proadrenomedulin; BOD: Index that combines Body mass, airflow Obstruction (FEV<sub>1</sub>% predicted), Dyspnoea (mMRC); ADOA: Index that combines the ADO index with MR-proADM; Updated ADOA: Index that combines the updated ADO index with MR-proADM; BODA: Index that combines the BOD index with MR-proADM; BMI: Body Mass Index; mMRC: modified Medical Research Council Dyspnoea grade; FEV<sub>1</sub>: Forced Expiratory Volume in 1 s.

<sup>a</sup> Corrected for BMI and congestive heart failure.

<sup>b</sup> Corrected for Age, BMI, mMRC and FEV<sub>1</sub> in liters.

<sup>c</sup> Corrected for Age.

<sup>d</sup> Corrected for BMI.

The HRs for the ADOA index risk categories remained almost unaffected after adjustment (3.3 (95% CI 2.3–4.8), 4.3 (95% CI 3.1–6.1) and 8.8 (95% CI 6.3–12.2) all  $p < 0.001$ ). Conversely, in the categories in which there was either high mortality risk based on MR-proADM (high MR-proADM/low ADO) or high mortality risk based on the ADO index (low MR-proADM/high ADO), the risk of survival was not significantly different ( $p = 0.180$ ).

Similarly, with the updated ADOA index there was no significant difference in survival between patients with high MR-proADM/low updated ADO risk and with low MR-proADM/high updated ADO risk ( $p = 0.519$ ), with HRs of resp. 3.1 (95%CI 2.2–4.5) and 3.4 (95% CI 2.5–5.1).

The univariate BODA index analysis already showed that patients with either high mortality risk based on MR-proADM (high MR-proADM/low BOD) or high mortality risk based on the BOD index (low MR-proADM/high BOD) had an almost equal increased risk of mortality compared to the low/low risk category. Although this finding remained unchanged ( $p = 0.059$ ), the risk of mortality seemed somewhat higher in the low MR-proADM/high BOD risk category (HR = 3.8;

95%CI 2.7–5.3) as compared to the high MR-proADM/low BOD risk category (HR = 2.7; 95%CI 1.8–3.9). High mortality risk based on both the BOD index and MR-proADM (high/high) showed a decreased risk (HR 5.8; 95%CI 3.9–8.4) of mortality after adjustment for confounders.

## Discussion

In this pooled assessment of two large European prospective observational cohort studies of patients with COPD, we could examine, for the first time, whether adding MR-proADM to the BOD, ADO and updated ADO indices increases the predictive probability of all three indices. We could demonstrate that patients with high MR-proADM levels had a significant increased risk of dying. Additionally, the combination of MR-proADM with ADO, updated ADO and BOD improved significantly the predictive power of the clinical indices.

The additive predictive value of MR-proADM to both the original updated ADO and BOD index supports the

underestimation of the systemic component in COPD in all three indices. The COTE index already showed that adding a comorbidity score to the BODE index increased its prognostic properties. However, the COTE index needs systematical recording of comorbidities, since it scores the presence of twelve comorbidities [5]. This makes it harder to apply in most clinical settings than the measurement of an MR-proADM level in stable COPD patients.

Compared to the predictive value of the BODE index, the BODA index, which includes the BOD index and MR-proADM, had a slightly lower predictive value based on the C-statistic (respectively  $C = 0.74$  and  $0.71$ ) [2]. Although the predictive power is slightly lower, MR-proADM measurement represents a good alternative to the 6MWD for mortality prediction. [7] Replacing the 6MWD by MR-proADM could potentially improve the feasibility of the BODE index, since difficulties in performing the 6MWT have been previously described (i.e., requirement of a long, flat, straight, enclosed corridor with a hard surface that is seldom travelled and must be 30 m in length; trained personnel; access to rapid, appropriate response to an emergency) [7]. The challenges associated with assessing the 6MWD lead to the development of indices refraining from measurement of the walking distances, such as the ADO index, a more simplified index that includes solely age, dyspnoea and airflow obstruction [4]. Based on the C-statistic, both the ADO and the updated ADO index had a numerically higher predictive value than the BOD index. Adding MR-proADM to both the original and the updated ADO index led to a comparable increased predictive probability as seen when adding MR-proADM to the BOD index (resp.  $C = 0.72$ ,  $0.70$ , and  $0.71$ ), suggesting that all three can be used without preference in every day clinical practice. And also the 1-year and 2-year mortality net correct reclassification of survivors and non-survivors when MR-proADM was added to the indices was comparable for all three indices. Next to this, the HR's of all separate and combined indices were similar when the analyses were stratified according to disease stage (GOLD stage I and II versus stage III and IV) (see [Online supplement](#)), suggesting that the risk for mortality in both mild to moderate and severe COPD patients is equally increased when patients are above the cut-off values of the indices.

The cut-off of MR-proADM in this pooled assessment ( $0.87$  nmol/L) was higher than the cut-offs previously described ( $0.71$  nmol/L) [9] ( $0.75$  nmol/L) [7]. On the one hand this might be due to the fact that the current, optimised cut-off represents the fourth quartile instead of the median. (Fig. 1). On the other hand, the difference in optimal cut-off could be additionally explained by the diversity of populations that were studied. The cut-off suggested by Zuur-Telgen et al. derived from a small subset of patients in the COMIC study that provided a paired plasma sample, both in stable state and at hospitalisation for an AECOPD. Due to this selection, patients deceasing during the hospitalisation or before reaching clinical stability were excluded from the analysis.

Our study has a few limitations. The main one is that we have not systematically recorded all co-morbidities in the COMIC study. Only common co-morbidities such as myocardial infarction, congestive heart failure and diabetes mellitus were noted, since these were probably related to MR-proADM due to its vascular activity and

related to survival. Therefore, we were not able to calculate the COTE index in this pooled assessment and to analyse the additive effect of MR-proADM to this index. Accordingly, we were not able to correct for other potentially confounding co-morbidities in the multivariate Cox proportional hazard analyses.

Although prednisolone has shown to inhibit MR-proADM levels [17], we do not expect systemic steroids to alter circulating proADM levels in the current study, since all patients were stable for at least 4 weeks before being included in this cohort study. This far, we are not aware whether the use of inhaled corticosteroids can also influence MR-proADM levels. We however do know that approximately eighty percent of the studied patients use an inhaled corticosteroid. Furthermore, we are not able to compare the BOD and BODA with the BODE score in this pooled assessment since we did not perform a 6MWT in the COMIC study. Previous data suggest that the performance of the BODE index is significantly improved by the addition of MR-proADM [7]. Next to this, we observed a difference in mortality between the COMIC and PROMISE-COPD study (respectively  $30.6$  and  $9.1\%$ ). A possible explanation might be that a considerable number of patients of the COMIC study were hospitalised for an AECOPD before the stable state level of MR-proADM and the other indices were measured. These patients having might have a worse prognosis. Additionally, the difference in follow-up (915 and 725 days, respectively) may have contributed to the difference in mortality. Furthermore, differences in the presence of other co-morbidities than the ones we studied may have contributed as well.

Finally, current results are pertinent to well-treated and characterised patients and might not reflect those observed in less severe, slightly undertreated patients.

Although MR-proADM has shown to contribute to prognostication, the perhaps most important question remains: How can prognostication improve patient care in COPD? Prognostication could be valuable if it could guide adjustment of care (more frequent contacts, additional medication, rehabilitation, and so forth) in high risk patients to eventually prolong survival. If, on the other hand, one hypothesizes that high MR-proADM levels combined with one of the indices predict inevitable death in the near future, this could perhaps aid in implementing end-of-life (palliative) care, because this is frequently instituted very late or not at all in many patients with COPD. Accordingly, whether optimisation of care or implementing end-of-life (palliative) care, based on risk stratification, could improve patient outcomes, should be evaluated in further randomized, controlled trials.

Furthermore, since most COPD treatments are not prescribed to modify mortality risk, but to reduce exacerbations, and improve symptoms and quality of life, it would be very interesting to also evaluate the predictive value of MR-proADM in combination with ADO and BOD for these important outcomes.

## Conclusions

In conclusion, adding MR-proADM to the BOD, ADO and updated ADO index increased the predictive power of all



three indices. MR-proADM is therefore a potentially valuable biomarker in stable COPD.

## Take home message

MR-proADM contributes to prognostication by multidimensional scores in stable COPD.

## Competing interests

The authors declare that they have no competing interests.

## Authors' contributions

Marjolein Brusse-Keizer contributed to the design of the COMIC study, to the analysis and interpretation of data and writing the article. Maaïke Zuur-Telgen contributed to the design of the COMIC study, to the interpretation of data and critically revising the article. Job van der Palen contributed to the design of the COMIC study, to the analysis and interpretation of data and critically revising the article. Paul van der Valk contributed to the design of the COMIC study, to the acquisition of patients, the interpretation of data and critically revising the article. Huib Kerstjens contributed to the design of the COMIC study, to the interpretation of data and critically revising the article. Wim Boersma contributed to the design of the PROMISE-COPD study, to the acquisition of patients and critically revising the article. Francesco Blasi contributed to the design of the PROMISE-COPD study, to the acquisition of patients and critically revising the article. Kostantinos Kostikas contributed to the design of the PROMISE-COPD study, to the acquisition of patients and critically revising the article. Branislava Milenkovic contributed to the design of the PROMISE-COPD study, to the acquisition of patients and critically revising the article. Michael Tamm contributed to the design of the PROMISE-COPD study, to the acquisition of patients and critically revising the article. Daiana Stolz contributed to the design of the PROMISE-COPD study, to the acquisition of patients, to the analysis and interpretation of data and critically revising the article.

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## Abbreviation list

ADM	adrenomedullin
ADO	age, Dyspnoea and airflow Obstruction
ADOA	age, Dyspnoea and airflow Obstruction and proadrenomedullin

AECOPD	acute exacerbation of COPD
BOD	body mass index, airflow Obstruction and Dyspnoea
BODA	body mass index, airflow Obstruction, Dyspnoea and proadrenomedullin
BODE	body mass index, airflow Obstruction, Dyspnoea and Exercise capacity
CI	confidence interval
COPD	chronic obstructive pulmonary disease
COTE	COPD specific comorbidity test
HR	hazard ratio
IQR	interquartile range
FEV <sub>1</sub>	forced expiratory volume in 1 s
GOLD	global initiative for chronic obstructive lung disease
mMRC	Medical Research Council Dyspnoea grade
6MWD	6-min-walking distance
6MWT	6-min-walking test
MR-proADM	midrange-proadrenomedullin
NRI	Net reclassification Improvement
SD	standard deviation
TRACE	time-resolved amplified cryptate emission

## Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.rmed.2015.02.013>.

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